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Synthesis of Thienothiopyranthiones by a New Molecular Rearrangement

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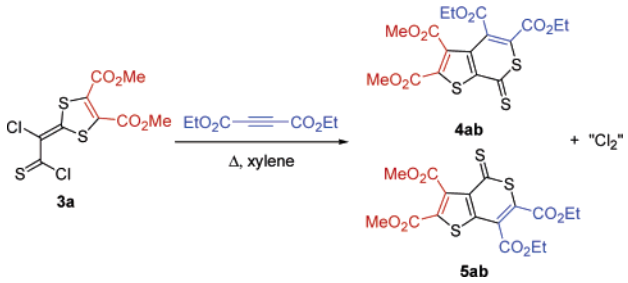
ABSTRACT



On heating with alkynes, the readily prepared 1,3-dithioles 3 undergo a new cycloaddition reaction and an unprecedented molecular rearrangement with loss of chlorine to give the first 7*H*-thieno[2,3-*c*]thiopyran-7-thiones 4 and 4*H*-thieno[3,2-*c*]thiopyran-4-thiones 5 whose structures were confirmed by X-ray diffraction. Unexpectedly, the different alkynes used to form 3 and to convert it into 4 and 5 were incorporated regiospecifically into the thiophene and thiopyran rings, respectively.

There is much current interest in the use and mode of action of 1,2-dithiole-3-thiones as cancer chemopreventive agents. 4-Methyl-5-pyrazinyl-1,2-dithiole-3-thione, oltipraz **1**, is one of the most promising agents against environmentally induced hepatocellular carcinoma[1] and other cancers.[2] 1,2-Dithiole-3-thione itself also protects against neoplasia.[3]

We wished therefore to extend the range of 1,2-dithiole-3-thiones available and to explore their chemistry further. One of their most interesting properties is to act as masked dipoles in 1,3-cycloaddition to electron-deficient alkynes.[4]

The first cycloaddition is accompanied by heterocyclic ring opening to give a 1:1 adduct (as in Scheme 1), which under more vigorous conditions adds a second alkyne in a Diels−Alder reaction to give a 1,4-dihydrothiopyran.[5]

We have recently shown[6] that 4,5-dichloro-1,2-dithiole-3-thione **2**, readily prepared from 3,4,5-trichloro-1,2-dithio-

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(1) Sudakin, D. L. *J. Toxicol., Clin. Toxicol.* **2003**, *41*, 195. Navamal, M.; McGrath, C.; Stewart, J.; Blans, P.; Villamena, F.; Zweier J.; Fishbein, J. C. *J. Org. Chem.* **2002**, *67*, 9406 and refs cited therein. Barriga, S.; Fuertes, P.; Marcos C. F.; Torroba, T. *J. Org. Chem.* **2004**, *69*, 3672 and refs cited therein.
(2) Yao, K.-S.; O'Dwyer, P. J. *Biochem. Pharmacol.* **2003**, *66*, 15. Miao, W.; Hu, L.; Kandouz, M.; Batist, G. *Mol. Pharmacol.* **2003**, *64*, 346.
(3) Kwak, M.-K.; Wakabayashi, N.; Itoh, K.; Motohashi, H.; Yamamoto, M.; Kensler, T. W. *J. Biol. Chem.* **2003**, *278*, 8135.
(4) Pedersen, C. Th. *Adv. Heterocycl. Chem.* **1982**, *31*, 63. Pedersen, C. Th. *Sulfur Rep.* **1995**, *16*, 173. McKinnon, D. M. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, Chapter 3.11, p 593.
(5) McKinnon, D. M.; Secco A. S.; Duncan, K. A. *Can. J. Chem.* **1987**, *65*, 1247. Fanghanel, E.; Palmer, T.; Kersten, J.; Ludwigs, R.; Peters, K.; von Schnering, H. G. *Synthesis* **1994**, 1067. Marcos, C. F.; Polo, C.; Rakitin, O. A.; Rees, C. W.; Torroba, T. *Chem. Commun.* **1997**, 879.

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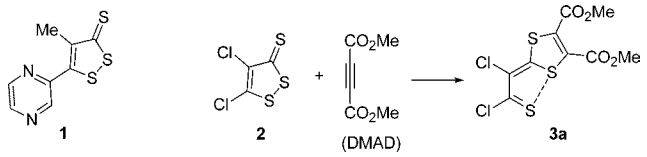
Scheme 1



lium chloride,[7] undergoes the same initial 1,3-cycloaddition to DMAD to give the adduct **3** almost quantitatively at room temperature. For an aliphatic thioacyl chloride, **3** is unusually stable but still highly reactive toward nucleophiles such as ortho-substituted anilines to give benzimidazole, benzoxazole, and benzothiazole derivatives of 1,3-dithioles.[6] Thioacyl chloride **3** and all the other thioacyl chlorides prepared (see below) are stable, deep red solids. Their stability was attributed to a significant interaction between the thiocarbonyl and a heterocyclic sulfur atom, which could reduce the electrophilicity of the thiocarbonyl group.[6] This is now supported by an X-ray crystal structure determination of **3a**, which shows the planarity of the quasibicyclic portion of the molecule, with a partial S···S bond length of 2.91 Å about midway between a normal S−S bond (2.05 Å) and the sum of its van der Waals radii (3.68 Å) (Figure 1).[8]

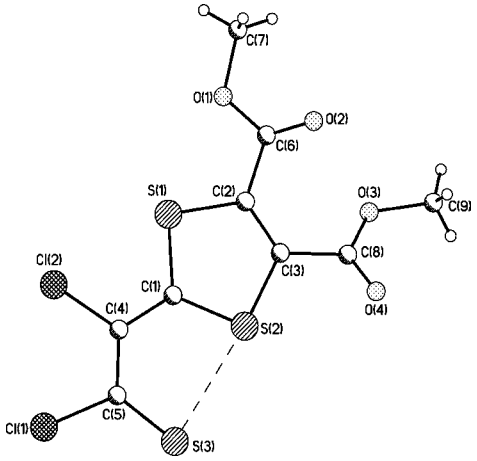


Figure 1. X-ray structure of molecule **3a**.

The presence of the S(2)···S(3) interaction is also reflected in the elongation of the S(2)−C(3) bond (1.749(3) Å) in comparison to S(1)−C(2) (1.740(3) Å). In addition, topological analysis of the electron density function $\rho(r)$ in **3a** according to B3LYP/6-31G* calculation has revealed the presence of the critical point (3,−1) ($\rho(r) = 0.17$ e Å^{-3}, $\nabla^2\rho(r) = 1.56$ e Å^{-5}) for S(2)···S(3) contact (2.945 Å), which according to Bader's "Atoms in Molecule" theory[9] serves as criteria of the chemical bond formation.

Treatment of 4,5-dichloro-1,2-dithiole-3-thione **2** with DMAD (3 equiv) in xylene at room temperature, followed by heating under reflux for 30 h, or heating the adduct **3a** with DMAD (2.5 equiv) in xylene for 30 h did not give the expected Diels−Alder adduct. The reaction took an entirely different course not observed in the absence of the chlorine substituents. It gave an approximately equimolecular mixture (^{1}H NMR spectroscopy) of 7*H*-thieno[2,3-*c*]thiopyran-7-thione **4aa** and 4*H*-thieno[3,2-*c*]thiopyran-4-thione **5aa** in 55% yield. The structures were fully supported by ^{1}H and ^{13}C NMR and mass spectrometry, and that of **4aa** was proved by X-ray crystallography (Figure 2).[8]

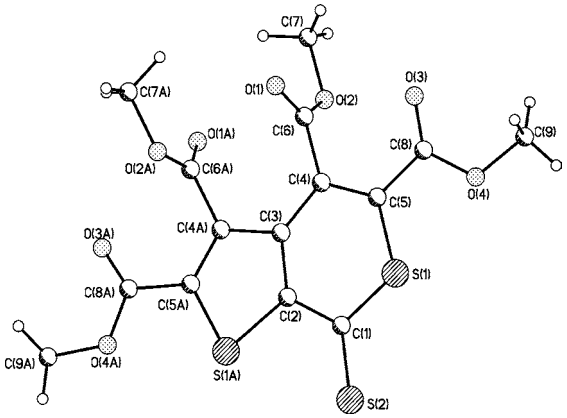
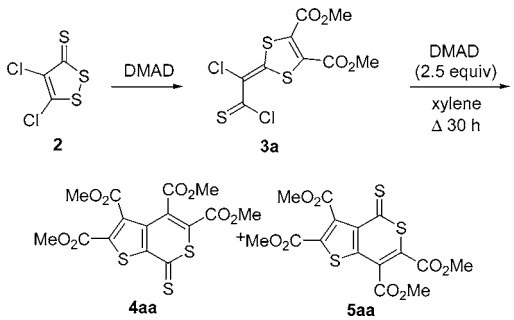


Figure 2. X-ray structure of molecule **4aa**.

Thus, overall, 2 equiv of DMAD added to dithiolethione **2** with expulsion of its two chlorine atoms (Scheme 2).

Scheme 2



When DMAD was replaced by diethyl acetylenedicarboxylate and by dibenzoylacetylene, equimolecular pairs of isomers (**4bb** + **5bb**) and (**4cc** + **5cc**) exactly analogous to **4aa** and **5aa** were formed in 50 and 32% yields, respectively.

(6) Ogurtsov, V. A.; Rakitin, O. A., Rees, C. W.; Smolentsev, A. A. *Mend. Commun.* **2003**, 50.

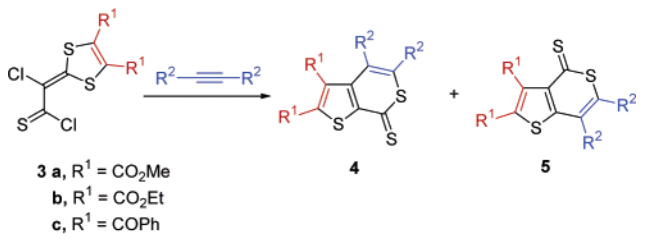
(7) Wentrup, G.-J.; Koepke, M.; Boberg, F. *Synthesis* **1975**, 525.

(8) X-ray data for **3a**, **4aa**, **5bb**, **5bc**, and **5cb** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 255373−255377 and are also available in Supporting Information.

(9) Bader, R. F. W. *Atoms In Molecules. A Quantum Theory*; Clarendron Press: Oxford, 1990

These isomers were separated by chromatography and recrystallization from methanol; all isomers **4** are red and **5** are yellow (see electronic spectra in Supporting Information). Products **4** and **5** are examples of relatively rare ring systems (Scheme 3).[10]

Scheme 3



Consideration of the most direct pathways from the 1,3-dithiole **3** and the second alkyne to the thienothiopyrans **4** and **5** suggested that the methoxycarbonyl groups would appear in the six-membered ring and the substituents on the second alkyne in the five-membered ring. To examine this, we repeated the reaction of each of the three 1,3-dithioles **3a**−**c** with each of the three alkynes R^2−≡−R^2, R^2 = CO_2Me, CO_2Et, and COPh. These nine reactions each gave a pair of isomeric thienopyrans in the yields shown in Table 1. Of these isomers, 14 of the 18 were isolated pure, and

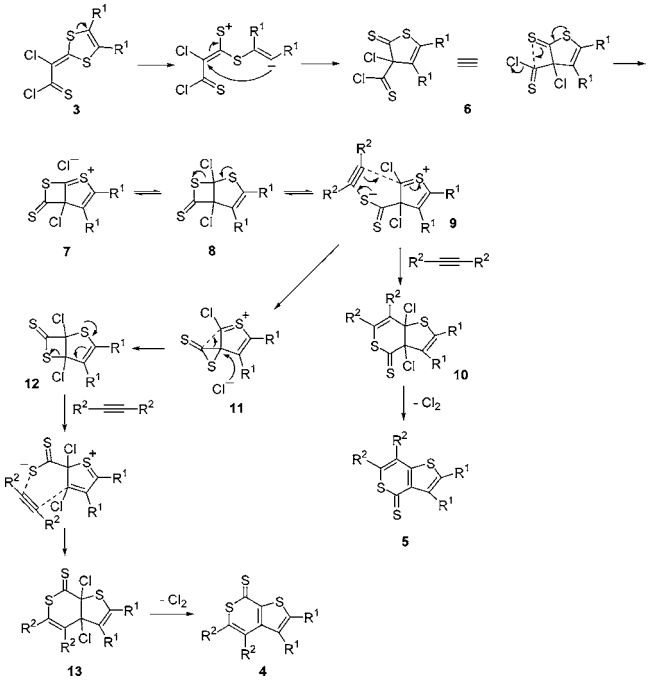
Table 1. Yields of **4** and **5** (Schemes 2 and 3)

		R^1		
		CO_2Me	CO_2Et	C(O)Ph
		55%	53%	33%
	CO_2Me	**4aa** **5aa**	**4ba** **5ba**	**4ca** **5ca**
		1:1	1:1	1:1
		57%	50%	43%
R^2	CO_2Et	**4ab** **5ab**	**4bb** **5bb**	**4cb** **5cb**
		1:1	1:1	1:2
		49%	30%	32%
	C(O)Ph	**4ac** **5ac**	**4bc** **5bc**	**4cc** **5cc**
		1:1	2:3	1:1

the structure of three more of them, **5bb**, **5bc**, and **5cb**, were proved by X-ray crystallography.[8] The structures of the isolated isomers were based on spectroscopic comparison of calculated and experimental ^{13}C NMR spectra. ^{13}C NMR spectra of various isomers of compounds **4aa** and **5aa** have been calculated by the method DFT/GIAO/B3LYP/6-31G*[11] (structure optimization with B3LYP/6-31G*). The Gaussian 98[12] program was used for calculations. The best match of experimental and calculated ^{13}C NMR data for compound **4aa** has been obtained for the structure confirmed by X-ray analysis (Figure 2). The results of comparing the experimental and DFT PBE[13] ^{13}C NMR data, obtained for compound **5aa** with a quite different structure (Scheme 3), also agreed with X-ray analysis. ^{13}C NMR signals of cyclic carbons for other isomers of **4** and **5** are similar to **4aa** or **5bb**, respectively. Additional support for the structures of the isomeric pairs came from their electronic spectra. All the red isomers **4** had characteristic bands at λ_{max} 254−268 nm (ϵ = 15 000−34 000), 336−348 nm (ϵ = 11 000−17 000), and 420−467 nm (ϵ = 4000−6700), and all the yellow isomers **5** had λ_{max} at 258−269 nm (ϵ = 23 000−36 000) and 373−397 nm (ϵ = 9500−16 600).

To our surprise, however, we found that in every case the substituents R^1 in **3** from the first alkyne to be reacted appeared in the *thiophene* ring of the products **4** and **5**, and the second alkyne substituents R^2 appeared in the *thiopyran* ring, implying an unexpectedly convoluted and unprecedented rearrangement that we are now investigating. One possible pathway is tentatively suggested in Scheme 4.

Scheme 4 [a]



[a] Typical Experimental Procedure. A mixture of **3** (2 mmol) and alkyne (5 mmol) was refluxed in xylene (20 mL) until compound **3** disappeared on TLC. The solvent was evaporated, and the residue was separated by column chromatography (Silica gel Merck 60). Single isomers were isolated by further column chromatography (Silica gel Merck 60) and/or crystallization of a mixture of isomers from methanol and/or from a mixture of hexane−toluene or hexane−ethyl acetate. Yields are given in Table 1.

In the reaction of thioacyl chloride **3** with the second alkyne, the intramolecular S···S interaction may suppress

(10) Brandsma, L.; Bos, H. J. *Recl. Trav. Chim.* **1969**, *88*, 732. Young, T. E.; Hamel, C. R. *J. Org. Chem.* **1970**, *35*, 816 and 821. Schuijl-Laros, D.; Schuijl, P. J. W.; Brandsma, L. *Recl. Trav. Chim.* **1972**, *91*, 785. Alam, I.; Thyagarajan, G. *Tetrahedron* **1973**, *29*, 1829. Grafing, R.; Brandsma, L. *Synthesis* **1978**, 578. Grafing, R.; Brandsma, L. *Recl. Trav. Chim.* **1980**, *99*, 23. Ramadas S. R.; Chandrakumar, N. S. *Phosphorus Sulfur* **1982**, *13*, 79. Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 7941. Marchand, E.; Morel, G. *Bull. Soc. Chim. Fr.* **1996**, *133*, 903. Mandal, S. S.; Chakraborty, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2639.

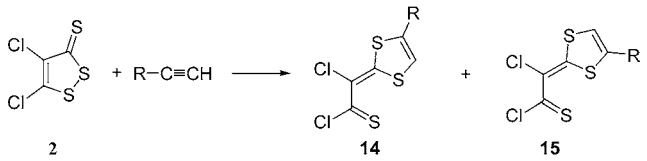
the Diels−Alder cycloaddition referred to above in favor of a sequence of heterocyclic ring-opening and -closing reactions. This could give initially the isomeric thioacyl chloride **6**, possibly in a concerted rearrangement; **6** could then collapse to the bicyclic systems **7** and **8**, the latter undergoing ring opening to give **9**, which could react with the second alkyne to give **10**. Aromatization of **10** by dechlorination would give the observed product **5**. Alternatively, **9** could rearrange via **11** to give the regioisomer (**12**) of **8**, which would react with the second alkyne in the same way via **13** to give the other observed product **4**.

The formation of the heteroaromatic products **4** and **5** from **3** plus an alkyne by the loss of Cl_2 suggested the formation and subsequent dechlorination of dichloro adducts of the aromatic systems such as **10** and **13**. In keeping with this, we found that treatment of *o*-xylene with Cl_2 gas gave 4-chloro-1,2-xylene and 3,3′,4,4′-tetramethylbiphenyl as the major products, and treatment of **3a** with DMAD in boiling *o*-xylene gave **4aa** and **5aa**, as before, together with exactly the same chlorination byproducts.

When $R^1 = R^2 = CO_2Me$, CO_2Et, or COPh, this new synthesis of thienothiopyrans **4** and **5** can be readily performed in one pot from the dithiole-thione **2** in xylene by adding the appropriate alkyne (3 equiv) at room temperature, followed by heating under reflux, to give **4aa**/**5aa** (57%), **4bb**/**5bb** (52%), and **4cc**/**5cc** (35%).

As expected, dithiole-thione **2** reacted similarly but much more slowly with monosubstituted alkynes R−≡−H (R = CO_2Me, Ph) (Scheme 5). Methyl propiolate required refluxing in toluene for 3 h, and phenylacetylene required refluxing in toluene for 32 h. Both gave inseparable mixtures of two red thioacyl chlorides **14a** and **15a** (ratio 1:3) and **14b** and **15b** (ratio 2:3).

Scheme 5



2 **14** **15**

a, R = CO_2Me; **b**, R = Ph

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Supporting Information Available: Experimental procedure and full characterization for compounds **3**−**5** and theoretical calculations for **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098; Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(13) Laikov, D. N. *Chem. Phys. Lett.* **1997**, *281*, 151.